Long-term outcomes of deep brain stimulation in Parkinson disease

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Abstract | The efficacy of deep brain stimulation (DBS) for Parkinson disease (PD) is well established for up to 1 or 2 years, but long-term outcome data are still limited. In this Review, we critically discuss the evidence on the long-term outcomes of DBS and consider the clinical implications. Although many patients are lost to follow-up, the evidence indicates that subthalamic nucleus DBS improves motor function for up to 10 years, although the magnitude of improvement tends to decline over time. Functional scores recorded during on-medication periods worsen faster than those recorded in off periods, consistent with the degeneration of non-dopaminergic pathways. Dyskinesia, motor fluctuations and activities of daily living in off periods remain improved at 5 years, but quality of life scores have usually fallen below pre-operative levels. The incidence and severity of dementia among patients receiving DBS are comparable to those among patients who receive medical treatment. Severe adverse events are rare, but adverse events such as dysarthria are common and probably under-reported. Long-term data on the outcomes of globus pallidus interna DBS are limited and mostly confirm the efficacy for dyskinesia. A trend towards offering DBS in the earlier stages of PD creates a need to identify factors that predict long-term outcomes and to discuss realistic expectations with patients pre-operatively.

[H1] Introduction

Deep brain stimulation (DBS) has become a routine treatment option for improving function and quality of life in patients with various movement disorders and for whom medical treatment has proved insufficient. The short-

term efficacy of DBS of the subthalamic nucleus (STN) or globus pallidus interna (GPi) among patients with Parkinson disease (PD) has been demonstrated repeatedly. However, far less data on long-term outcomes of the surgery have been collected.

Twenty-five years after the first report of unilateral DBS of the STN (STN DBS)[1], studies of long-term outcomes of DBS are emerging, thereby providing a body of evidence on its effectiveness and its safety. This evidence is important, as it should be considered when the timing and appropriateness of surgery are discussed with a patient who is likely to need long-term therapy.

Here, we critically review the published evidence that relates to long-term outcomes of DBS for PD and consider the clinical implications of this evidence. We focus on studies in which the follow-up period was at least 5 years because the evidence suggests that this point is important for disease progression and because the number of articles with longer follow-up periods is limited.

[H1] Development of DBS

The modern era of DBS began in the 1980s when Benabid et al. published studies in which patients with PD who had drug-resistant tremor were successfully treated with chronic, high-frequency stimulation of the ventro-intermediate nucleus of the thalamus[2,3]. Before this work, stimulation had been performed mainly during surgical procedures, such as thalamotomy, to test the accuracy of electrode placement in the brain[4]. The advent of implantable pulse generators capable of delivering long-term high-frequency stimulation enabled the approach used by Benabid et al., and use of thalamic DBS subsequently started to replace thalamotomy, with the advantages that the stimulation dose and location could be titrated to maximize the tremor response but minimize stimulation-provoked side effects. In addition, DBS made bilateral procedures safer than bilateral thalamotomy.

STN DBS was subsequently developed, and the first series of three patients with bilateral STN was published[5]. This work has since been supported by an increasing number of open-label series and randomized trials[6-9], all of which have demonstrated an advantage of STN DBS over conventional medical

treatment during short-term follow-up periods. Work conducted in parallel has also shown that chronic DBS of the GPi (GPi DBS) can lead to benefits in motor control in PD. Overall, very little detectable difference in quality of life improvements has been seen between the two procedures[10-13], although most investigators conclude that STN DBS has greater beneficial effects on symptoms in off periods than GPi DBS in PD (Box 1), thereby enabling reductions in medication for these symptoms, whereas GPi DBS reduces L-dopa-induced dyskinesia to a greater extent.

[H1] Assessment of long-term outcomes

Assessment of the long-term effects of DBS is heavily dependent on the outcome measure chosen. In most studies, the reported outcomes are the effects of DBS on the severity of PD (assessed with the Unified Parkinson's disease rating scale (UPDRS) part II (activities of daily living), part III (motor subsection) and part IV (complications of therapy), and/or one of several available dyskinesia rating scales) in off periods and on periods. These measures provide a clear cross-sectional snapshot of the therapeutic efficacy, but do not necessarily provide a complete assessment of patients' true daytime function. An alternative approach is to focus on the patient's perspective and measure the overall quality of life by use of the disease-specific PDQ39 questionnaire. However, long-term quality of life data has been collected in only a limited number of studies.

Adverse outcomes of long-term DBS are also important and must be assessed. Adverse events are mostly assessed by clinical examination and listening to the patient's observations. Adverse effects of the implantation surgery are fortunately rare, and rates of symptomatic haemorrhage and infection are generally low. By contrast, adverse effects of stimulation, such as dysarthric speech, swallowing disturbances, freezing of gait and balance disturbances, are increasingly being recognized and can occur with use of stimulation parameters that are optimal for improving tremor, rigidity and bradykinesia. PD progression undoubtedly continues despite DBS surgery, so distinguishing stimulation-induced adverse effects from disease progression can be difficult; the most convincing demonstration that adverse effects are caused

by the DBS is resolution of the effects with adjustment of stimulation parameters.

[H1] Reported long-term outcomes

We identified 15 studies of STN DBS in which outcome measures included UPDRS part III scores that were recorded pre-operatively and after 5 years (to enable analysis of the motor effects of DBS) when patients were in off periods but receiving DBS[14-28]. We identified only two similar studies of GPi DBS (reported in three articles), which we therefore consider separately[29-31]. Of the 15 STN DBS studies, five included patients for whom follow-up was 8–11 years[20-23,27]. Detailed bradykinesia, rigidity and tremor sub-scores of the UPDRS were reported in 11 of these 15 studies[14, 16, 17, 19, 21-26].

In other studies, long-term outcome measures of STN DBS other than UPDRS part III have been included, and we include these studies in our discussion. Given the paucity of long-term data on GPi DBS, which hinders the inevitable desire to compare the effects of stimulating these two targets, we include a brief discussion of short-term, randomized comparisons.

[H2] STN DBS

Across the 15 identified studies of STN DBS, 5-year outcomes for a total of 551 patients are reported, out of 923 patients who underwent electrode implantation at baseline (Supplementary Table 1). Ninety-nine patients died, but the causes were unrelated to DBS in the vast majority of cases. Other patients were lost to follow-up, were followed up in other centres or had become too disabled to come for assessment because of PD progression or other illness such as stroke. The mean age at surgery was 52.9–61.4 years (depending on the study), the average duration of disease varied from 6.8 years to 16.4 years, and most studies included patients with a disease duration >10 years. There was an excess of men included in most studies. The reported long-term outcomes across these studies are discussed below.

[H3] Motor function

The most consistently reported outcome measure was the UPDRS part III motor score recorded when patients were in off periods or on periods (Fig. 1). In all studies, the UPDRS off-period score when stimulation was switched on was significantly lower (indicating an improvement of symptoms) at 1 year and 5 years than at baseline, and at longer follow-up time points in the few studies that included these. Nevertheless, scores clearly indicate that the benefits decrease with longer follow-up. UDPRS on-period scores are generally worse than at baseline by the 5 year time-point, despite some improvements seen at 1 year. This observation probably reflects the fact that STN DBS is a symptomatic treatment of the off periods and does not improve symptoms during the on period that reflects the dopa-sensitivity of symptoms at this stage of the disease.

In eleven studies sub-scores for motor improvements (tremor, rigidity, bradykinesia and axial features) could be calculated[14, 16, 17, 19-26] (Supplementary Table 2). These data clearly demonstrate that substantial DBS-induced improvements in rigidity and tremor during off periods are maintained at 5 years and beyond, whereas beneficial effects of DBS on bradykinesia and axial signs seen at 1 year have started to decline by 5 years. By contrast, in the on periods, akinesia and axial signs have generally worsened in comparison with baseline by 5 years. In one study that included 18 patients who had received DBS for an extended period, symptoms in the off period were assessed in these patients by a rater who was blinded as to whether STN stimulation was on or off; **[Au: I have tried to clarify the explanation of the first blinded study further. Is the meaning of this wording correct?]** the results indicated that at a mean of 10 years after DBS surgery, DBS significantly improved UPDRS part III scores, particularly those for tremor, rigidity and limb bradykinesia[21]. In another study with a similar design and that included 29 patients who were receiving STN DBS, substantial improvements over baseline scores for tremor (85% improvement) and rigidity (66% improvement) were seen at 5 years. At the same time point, improvements in bradykinesia were smaller (38% relative to baseline), and gait and balance scores were approaching baseline severity[19]. In a multicenter, double-blinded assessment study of 31 patients, STN DBS was associated with significant improvements in the off period relative to baseline at 5–6 years after implantation[29].

The effects of STN DBS on axial signs in PD have also been studied in a meta-regression analysis. This study showed that "postural instability/gait disturbance" (PIGD) in the off period would, on the basis of extrapolation, worsen to the pre-operative state after 9 years, whereas the severity of PIGD in the on period would reach pre-operative severity after only 2 years[32]. These findings confirm that STN DBS provides symptomatic treatment for the off periods and that the disease continues to progress.

In four studies, patients who were receiving STN DBS were assessed in an off period and after the stimulation had been stopped for a short period[17, 21, 22, 33]. Surprisingly, this approach identified no significant difference in UPDRS part III scores at 5–10 years when compared with off-period scores at baseline. Worsening relative to baseline was expected, but given that the data were collected only a short time after stimulation was stopped, this observation more likely indicates that the full effects of stimulation have not completely 'washed out' rather than a neuroprotective effect of stimulation.

Of further interest is that the response to levodopa decreases over time in patients who are receiving STN DBS. In one study, the percentage improvement in the off-period UPDRS III score after levodopa was 68% at baseline, 60% at 1 year, 45% at 5 years and 37% at 9 years[22], and similar figures have been found in other studies[18, 34]. However, this effect is probably related to disease progression, as the rate at which the on-period UPDRS part III score declines has been shown to be similar to that of a control group who did not receive DBS[35].

Other measures have been used to assess long-term outcomes of STN DBS. Use of the UPDRS part IV has demonstrated that STN DBS significantly improves dyskinesia[14-16, 18, 19,21-23, 26] and motor fluctuations, and that these improvements mostly persist beyond 5 years[15, 16, 18, 19, 21-23]. In one study, use of diary data also revealed improvements in motor fluctuations and dyskinesia up to 5 years after STN DBS[28].

In one study of long-term STN DBS outcomes, a non-operated comparator group was included. Individuals in this group were patients who had been assessed as suitable for DBS but subsequently underwent alternative medical interventions for reasons unrelated to their PD[36]. In this long-term comparison, in which the average follow-up period was 6 years, improvements in motor

fluctuation, dyskinesia and activities of daily living in the off period were greater among the group who received STN DBS than among the medically treated group. Comparison of three groups of 20 patients who were treated for 5 years with STN DBS, levodopa carbidopa intestinal gel (LCIG) or oral medical therapy showed that DBS and LCIG were superior to oral therapy for reducing the duration of off periods and improving dyskinesia at 5 years[37]. Less deterioration in activities of daily living was observed in the STN DBS and LCIG groups than in the oral medical therapy group. Furthermore, STN DBS was superior to LCIG for improving dyskinesia and was associated with fewer adverse events.

[H3] Activities of daily living and quality of life

Long-term improvements in the activities of daily living subscale (UPDRS part II) during off periods have been demonstrated in several studies. Improvements have consistently been seen for up to 5 years[14, 15, 17, 19, 21, 22, 28], but longer term results are more variable: for example, in one study, scores were still improved relative to baseline at 10 years[21] but, in another study, complete loss of improvement was seen at 9 years[22]. However, UPDRS part II on-period scores have usually been worse than at baseline even at 5 years confirming the observations made for other measures[14,15, 17, 19, 21, 22, 28].

Quality of life has been assessed with the PDQ39 in several studies, which have uniformly shown that the improvements from baseline that are seen at 1 year have been lost by 5 years[23, 25, 28, 38]. Use of the PD Quality of Life (PDQL) scale in another study has demonstrated that a significant improvement (20%) over baseline was maintained for up to 5 years, although the magnitude of the improvement declined between years one and five[19].

[H3] Non-motor symptoms

Although PD is primarily considered to be a movement disorder, several non-motor symptoms can also occur, and the effects of DBS on these symptoms must also be considered. Long-term studies on non-motor symptoms have largely focused on cognition and psychiatric conditions.

Separating the effects that PD progression and DBS have on cognition is a major challenge that requires either a control group or a clear and reproducible

difference in cognitive function between stimulation-on and stimulation-off conditions. In one study of 16 patients who received STN DBS for PD, 31% had developed dementia by 6–9 years after DBS implantation surgery compared with 45% of patients in a comparable, non-operated population[39]. In another study, the rate at which dementia developed after STN DBS was estimated at 35.7 per 1,000 person-years of follow-up; this rate is similar to that among non-operated patients with PD at the same stage of disease[40].

Despite these encouraging results, subtle impairments in cognition have been consistently associated with STN DBS. A decline in verbal fluency has been observed in most studies in which this parameter has been quantified[41]. One study has demonstrated that verbal fluency among patients who receive STN DBS is significantly worse at 8 years after initiation of the treatment than among comparable controls with PD who were eligible for surgery but declined[42]. As expected, cognitive decline was seen in both groups over the follow-up but no cognitive measures other than verbal fluency differed between them even at 8-year follow-up. Similarly, many studies in which the Mattis Dementia Rating scale, a global measure of cognition, has been used to assess patients receiving DBS have found that cognitive function is generally unchanged at 1 year after initiation of DBS but gradually declines by 5 years[14, 15, 17, 23]. This decline could be predicted to some extent on the basis of the degree of impairment in executive function at baseline[28].

Studies of the effects of STN DBS on psychiatric features of PD have shown that these symptoms can either reduce or occur for the first time after STN DBS; many investigators in this field believe that these effects are strongly related to the extent and direction of changes in medication[43]. Several studies have shown that depression scores improve with STN DBS, although these improvements tend to wane with longer follow-up[14, 15, 17, 19, 22, 23, 25, 28]. By contrast, apathy and fatigue scores tend to increase with STN DBS and remain increased in the long term[39,44]. Scores for these features are higher among patients receiving STN DBS than among comparable non-operated patients with PD[39,44].

As for psychiatric symptoms, changes in impulsive compulsive behaviours in response to STN DBS can vary: case reports and case series have detailed both

complete resolution and the first emergence of these behaviours. These effects are also likely to be related to the extent to which medication is reduced[43,45]. A long-term study has shown that hyperdopaminergic behaviours, such as hypomania, gambling and compulsive shopping, were all reduced after STN DBS in a series of 69 patients with PD over a mean follow-up of 6 years[44].

The long-term effects of STN DBS on other non-motor symptoms of PD have been studied to a lesser extent. In a cohort of 24 patients with PD, STN DBS improved PD-related pain for up to 8 years[46]. In another series, sleep diaries revealed that patients who received STN DBS had longer periods of night-time sleep at 5 years after implantation than at baseline[28].

[H3] Adverse effects

Various long-term adverse effects of STN DBS have been observed but, on the basis of our experience, these effects seem to be vastly under-reported in the published literature. Adverse effects were described in detail in only five long term studies (Table 1) [14, 15, 17, 19, 20]. Acute complications that arise from the initial surgery are rare but can be life-threatening. Similarly, hardware complications, such as lead fractures and device malfunctions, are rare — estimated rates of such events are 1.4% and 0.5%, respectively — but need to be dealt with promptly[47].

However, in our experience, long-term adverse effects that do occur, such as deterioration of speech or balance, eyelid apraxia and weight gain, are often not formally reported, either because their relationship with DBS is not recognized or because clinicians fail to routinely document their presence. In one study of adverse events of DBS in 123 patients with movement disorders, **[Au: Addition made to clarify that the patients not referred to in the following had non-PD movement disorders]** 82 of whom had PD, 5% of patients with PD had severe long-term adverse events, and 23% of the 78 patients who received STN DBS had non-reversible adverse events[48].

The available data indicate that STN DBS has no adverse effects on long-term survival, which is broadly similar to[16, 35] or slightly better than[49,50] that among comparable non-operated patients with PD. Most deaths among patients receiving STN DBS are unrelated to the DBS surgery. However, careful

documentation shows that the percentage of intelligible speech declines with use of STN DBS, from 91.9% of spoken words understandable at baseline to 80.8% at 1 year, 70.2% at 5 years and 63.5% at 8 years[23]; this rate of decline was higher than that in a non-operated group. **[Au: Addition made to clarify what the rate of decline was compared with. OK?]** Average weight gain among 47 patients who received STN DBS was 7.2 kg at 4.7 years after surgery; 57.4% of patients were overweight or obese at the last follow up, compared with 34% before DBS[51]. One particularly serious adverse event is a withdrawal syndrome: withdrawal of DBS in patients in whom the duration of disease and stimulation has been long can be life-threatening as it can lead to a severe parkinsonian state that medications are not sufficient to control[52], and it should be managed promptly by restarting effective stimulation .

[H3] Medication changes

In the 15 studies of STN DBS that include long-term data, the mean baseline levodopa equivalent dosage (LED) was 1,106 mg daily (Supplementary Table 3) and the mean percentage reduction in dose after DBS surgery was 52% at 1 year (range 39–83%) and 45% at 5 years (range –11–63%). Among the few studies with longer follow-up periods, the dose was reduced by a mean of 42% at the end of follow-up (range 21–60%). This reduction in dopaminergic medication is a good indication of how effectively STN DBS improves PD symptoms. The reduction also minimizes the adverse effects of those medications, in particular dyskinesias and hyperdopaminergic behavioral problems. **[Au: Wording adjusted slightly. OK?]**

[H3] Responses to electrical parameters

Most patients in long-term studies of STN DBS received monopolar stimulation through a single contact on each electrode, but some received bipolar or double monopolar stimulation (Supplementary Table 3). The mean amplitude of stimulation at 1 year was 2.8 V, which increased to 3.15 V by 5 years. This increase is small, and probably reflects that adjustments can be made as the disease progresses, **[Au: OK?]** although it could also reflect that local changes

take place around the electrode, and this effect is indicated in one study in which therapeutic impedance decreased over time[27]. **[Au: Changes to wording OK?]**

In several studies, adjustment of the frequency of stimulation has improved control of symptoms. In three studies[17, 20, 21], use of low-frequency (60 Hz) stimulation in long-term follow-up alleviated freezing of gait and/or dysarthric speech in 64.3% of patients[20]. In another study, an increase in stimulation frequency improved tremor in 55.6% of patients[20].

[H2] Prediction of long-term improvement

An understanding of the factors that affect whether STN DBS is likely to provide long-term improvements would be valuable in making decisions about which patients to treat and when. Intuitively, an important factor is the accuracy with which the active stimulating contact is placed within the STN, and this hypothesis has been confirmed in one study in which 5-year outcomes of STN DBS were better if at least one stimulating contact was located in the sensorimotor part of the STN than if none were[23]. **[Au: OK?]** In the same study, younger age at disease onset, worse pre-operative off-medication UPDRS score and more severe fluctuations in symptoms between on and off periods were all associated with greater long-term improvement[23]. In another study, pre-operative scores for gait disturbance in off periods inversely correlated with 10-year motor outcomes of DBS[21], and this observation was confirmed with 8-year follow-up data in another study[20].

In one study of 110 patients who received STN DBS, the roles of age and disease duration in determining long-term outcomes were examined[24]. Patients aged >65 years had poorer 5-year outcomes than younger patients, particularly with respect to axial scores, and a longer disease duration at the time of DBS surgery was associated with a worse Schwab and England (activities of daily living) score at follow-up. A comparison of patients who were still independent in activities of daily living (Schwab and England score >70) at 5 years after DBS surgery with patients who were not demonstrated that the independent variables associated with long-term independence were age at surgery and pre-operative Mini Mental State Examination (MMSE) and Schwab and England scores in the off period[53].

[H1] GPi DBS

To date, the outcomes of GPi DBS in PD beyond 5 years have been assessed in only two studies[29, 31]. In the first of these studies[31], six patients (from an initial cohort of 11 individuals) experienced improvements in UPDRS part III scores in off periods that were maintained at 3 years (a reduction of 43%), but the only remaining benefit by 5 years was an improvement in rigidity. Four of the original 11 patients who lost an initial benefit from GPi DBS subsequently underwent STN DBS, which renewed their improvement. In patients who continued to receive GPi DBS, beneficial effects on levodopa-induced dyskinesia were maintained up to 5 years.

In contrast to these generally negative findings, in another study of 16 patients, UPDRS part III scores in the off period were reduced by GPi DBS from a mean baseline of 52.2 to a mean of 33.9, even after 5–6 years of the treatment[29]. Furthermore, compared with patients who had undergone STN DBS, fewer patients exhibited cognitive decline, speech difficulties or gait and balance disorders. The patients who were included in this study had not been randomly allocated to receive the different forms of DBS, which limits the extent to which conclusions can be drawn from the comparison.

Given the lack of studies and the contradictory findings, further studies of the long-term outcomes of GPi DBS are clearly needed. Existing data clearly show that GPi DBS has a sustained beneficial effect on levodopa-induced dyskinesia, but the extent to which symptoms of PD in the off period can be improved has been variable.

[H1] Comparison of STN DBS and GPi DBS

Two randomized trials have been conducted to directly compare the outcomes of STN DBS and GPi DBS[10, 12], although the longest follow-up published to date is only 36 months[11,13]. In one study, motor symptoms in the off period improved to a greater extent among patients who received STN DBS than among those who received GPi DBS[13], whereas in another study, motor scores in on periods were better with GPi DBS than with STN DBS[11]. No differences in cognition or

psychiatric outcomes were found between patients who received STN DBS or GPi DBS at 3 years[54].

Without randomized studies, direct comparisons between GPi DBS and STN DBS are difficult, and the longer term outcomes of previously performed trials are therefore eagerly awaited[11,13]. In the meantime, patients continue to be selected for STN DBS or GPi DBS on the basis of experience and prejudices at individual centres.

[H1] Limitations

Existing studies of the long-term outcomes of DBS are limited by several factors. The most obvious issue is that the published data are potentially biased owing to missing data as a result of patient deaths from PD, comorbidity, loss to follow-up, follow-up at other centres and disease severity preventing patient visits for assessment.

In most studies to date, the comparison made is between baseline and follow-up severity of PD, which is of limited value for informing patients on long-term outcomes given that PD is a neurodegenerative process. Consequently, comparable non-operated control groups are needed in future studies. One possibility is a head-to-head long-term comparison of DBS with conventional treatment or with another advanced therapy, such as apomorphine or duodopa. However, the choice of the comparator arm challenges the existing ability of a patient to influence the choice of treatment according to their preference, and the ability of a clinician to recommend which treatment they suspect a patient will do better with; both abilities would disappear in a randomized comparison of treatments. **[Au: Change to wording OK?]** The data that are currently available come from either randomized studies that are limited to 1 or 2 years of follow-up[6-9] or non-randomized, often retrospective studies[36, 37, 55]. These studies generally indicate superiority of DBS over conventional treatment, levodopa–carbidopa intestinal gel and apomorphine, but in the absence of long-term data from a randomized trial, these comparisons should be interpreted with caution.

Another limitation is that interpretation of long-term data is confounded by medication changes. Assessment in the off period is generally performed after an overnight withdrawal of medication and therefore provides only a surrogate

measure of the true underlying PD severity. As a result of DBS, major changes are often made to medication, so the effect of overnight withdrawal at different time points might not be equivalent. Furthermore, the alleviation of symptoms as a result of medications (in the on period) can reduce after STN DBS, and it is unclear whether this reduction is related to disease progression and the emergence of dopa refractory signs, a reduction in dopa responsiveness owing to DBS, or use of a lower dose of medication[34]. In one study, the rate of progression in patients receiving DBS was compared with that in a non-operated population and no difference was seen[35], but this finding will need to be confirmed in a larger sample. Therefore, within these limitations, the existing evidence suggests that STN DBS maintains usual on-period function for only 2–5 years, whereas the treatment maintains off period improvements for 9–10 years.

[H1] Current and future clinical implications

The published evidence consistently supports the idea that 'well-selected' patients (those who are likely to benefit from surgery and are unlikely to experience adverse effects on the basis of their clinical presentation) gain short-term improvements in quality of life as a result of DBS surgery compared with conventional medical treatment. These benefits persist for the first years after electrode implantation, and additional benefits in the core motor aspects of PD (tremor, rigidity and bradykinesia) persist to 8–10 years. This evidence therefore strongly supports the use of DBS in patients with marked disability as a result of these symptoms.

Nevertheless, the evidence also makes clear that DBS does not prevent disease progression or the development of axial problems, such as disturbances of gait, balance and speech, or cognitive disability, which become the major determinants of quality of life in the long-term. Furthermore, chronic STN DBS can cause adverse effects, such as dysarthric speech and freezing of gait in particular, and these effects must be recognized by centres that provide DBS services because they might be modifiable with adjustment of stimulation parameters[17, 20, 21, 56], medication changes or electrode repositioning. Some patients will develop irreversible and disabling axial deficits, and the relative contributions of disease progression and stimulation can be impossible to

disentangle. The combination of disease progression and chronic DBS has led to increased recognition of a new PD phenotype characterized by patients who are no longer disabled by tremor, rigidity or dyskinesia but who have poor-quality speech, frequent freezing and falls.

Currently, candidates for DBS are considered to be **[Au: Changed wording because "defined" implied that there is a written definition somewhere. Change OK?]** — according to outcomes in clinical series — people with PD who are younger than 70–75 years, have a good motor response to levodopa, have little or no medical or psychiatric comorbidity and have no major abnormalities on pre-operative MRI brain scans[57], but who have some degree of disability (usually motor fluctuations or dyskinesia) that are refractory to adjustments of non-invasive therapies. Within these broad criteria, some patients are presumably likely to have better long-term outcomes than others, and identifying the factors that predict who these patients are would be helpful. One study demonstrated that patients over the age of 65 years developed more severe axial signs during the follow-up[24], an observation that certainly warrants further study. In addition, data from the Parkinson Progression Markers Initiative study published in 2016 indicate that patients who are older at symptom onset have a greater burden of motor and non-motor symptoms even in the absence of DBS[58], so the long-term outcomes of DBS in older patients might be expected to be unfavourable. Furthermore, some series indicate that for patients with the most severe pre-operative gait difficulties, the long-term benefits of DBS are limited[20, 21].

Given that the risks of surgery are lower in younger people with less brain atrophy and that the evidence indicates that the benefits of DBS (at least appendicular motor benefits) are more sustained in younger patients, DBS in patients at early stages of disease (with independent functioning and good quality of life) is being considered[8]. However, the 'very-long-term' effects of DBS (including the possibility of reduced dopa responsiveness) are unknown and would be relevant to patients who undergo surgery early in the disease course. The decision to undertake surgery in any individual patient, must therefore consider the potential of both acute and chronic adverse effects of DBS, as well as

specifically addressing the severity of symptoms at baseline and individual patient expectations.

Knowledge of patient heterogeneity is also increasing and could become increasingly relevant in the surgical decision process. For example, the effects of specific genetic risk factors for PD on the long-term outcomes of patients who undergo DBS are the focus of ongoing studies. **[Au: The trial on the clinicaltrials.gov website can be cited – I will add this to the references when I receive manuscript back from you]** There are some data to suggest that patients with mutations in *GBA1* have more aggressive disease[59, 60] and that, consequently, their disability progresses to a greater extent after DBS than in those with other forms of PD. Whether this effect simply reflects a more aggressive underlying disease process in these individuals or indicates an interaction between genotype and the surgical intervention requires further study, ideally in a randomized study.

Another uncertainty that affects clinical decisions is the precision with which electrodes must be placed to ensure good long-term outcomes. The limited amount of data currently makes it difficult to gauge how strong the relationship is between the accuracy of electrode placement and long-term improvements in quality of life. Furthermore, stimulation-induced side effects, which might result from inaccurate placement of electrodes, can limit the beneficial effects from DBS and can become an increasing challenge with long-term follow up. The development of improved technology, such as directional DBS electrodes and closed-loop or adaptive DBS, alongside improved imaging and targeting platforms might improve consistency of outcomes.

For patients with PD that is in the most advanced stages (with significant gait, balance and cognitive impairments) outcomes of DBS at conventional targets are not good. For this reason, there is interest in DBS of other brain regions, such as the pedunculopontine nucleus or the nucleus basalis of Meynert[61-64], with the hope that stimulation will enhance neuronal network activity. To date, the short-term outcomes of these approaches have been variable, and long-term follow up of patients involved in these studies has not be done. Consequently, these approaches should currently be considered as experimental.

Network-targeted DBS is also being tested in other neurodegenerative disorders, such as Alzheimer disease (AD). As in advanced PD, the aim in AD is to enhance the activity of underactive brain networks by targeting either the fornix or the nucleus basalis of Meynert[65,66]. Early results indicate that the effects are very mild and inconsistent[65,66], in contrast with the marked improvements that were seen in the early trials of STN DBS. These results cast some doubt on the future of DBS for dementia, although the challenges associated with increasing neuronal activity might be quite different from those associated with suppression of abnormal neuronal firing patterns.

[H1] Conclusions

The current evidence indicates that STN DBS can improve motor function in PD for over 10 years. Nevertheless, many patients enrolled in studies are lost to follow-up, and outcomes are variable between patients. Dyskinesia and motor fluctuations often remain improved, whereas improvements in axial symptoms and quality of life in the first few years tend to decline over time. Age, severity of PD and the position of electrodes are important predictors of long-term improvement. In contrast to STN DBS, GPi DBS mostly improves dyskinesia in the long-term.

In the context of these caveats, the discussion of long-term pros and cons and the timing of surgery is, for many individuals, irrelevant because of the urgency of their clinical situation and lack of alternative options. For an individual who has severe disability despite multiple attempts at controlling symptoms with conventional medication, DBS has the potential to provide long-term symptom relief, and the available data largely support use of this clinical approach. By contrast, a young patient for whom conventional medication provides excellent control of symptoms should not be led to believe that the evidence for long-term benefits of DBS is yet sufficient to conclude that initiation of DBS at an early stage is the best option.

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Review Criteria

A PubMed search was performed using the terms “Deep Brain Stimulation”, “Subthalamic nucleus” and/or “STN”, “Globus Pallidus Interna” and/or “GPi” “Parkinson’s disease” and “Long-term”. From the 284 articles obtained from this search, we identified studies that included clinical scores at 5 years of follow-up or longer. Further studies were identified from article bibliographies. To avoid duplication caused by several articles published by the same DBS unit, only articles providing the most recent relevant data were referenced. Multi-centre studies that overlapped with published data from single centres were not included. From each eligible study, directly comparable data were extracted to enable calculation of mean changes in motor and non-motor outcome measures from baseline to 1-year, 5-year and longer (8–11-year) follow-up periods.

[Au: We cannot be thanked in the acknowledgements, although I appreciate that you’d like to. I’ve therefore removed the acknowledgements section.]

Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

P.L. and T. F. have received honorarium and travel expenses for lectures from Boston Scientific and Medtronic. T.F. has also received honorarium from BIAL, Britannia and Profile Pharma.

[Au: I’d be grateful if you could add these points.] [Au: Please provide a list of up to 6 brief bullet points, each no more than 2 sentences long, highlighting the take-home messages of the Review.]

Bullet Points

STN DBS can provide long-term improvement in motor function in patients with PD.

STN DBS does not prevent the neurodegenerative processes of PD and therefore quality of life scores have usually fallen to pre-operative levels by the 5 year time point.

Deterioration in quality of life often reflects the emergence of dopa refractory/ stimulation resistant motor and non-motor features of the disease, particularly gait, balance and speech.

Distinguishing stimulation induced adverse effects from disease progression, requires experience and a systematic approach to stimulation adjustments, and

awareness of the potential inter-relationship with changes in dopaminergic medication.

Important predictors of long term outcome are patient selection, precision of electrode targeting and experienced stimulation and medication adjustment.

[Au: I have put together the supplementary tables in one separate document, also attached.]

Table 1 | Adverse events reported in five studies of subthalamic nucleus deep brain stimulation[14,15,17,19,20] with ≥5 years follow up.

Type of adverse effect	Adverse effect	Number of patients
Permanent	Weight gain	90
	Dysarthria	50
	Eyelid apraxia	38
	Death (total)[a]	22
	Apathy	22
	Cognitive decline or dementia	20
	Depression	14
	Dyskinesia	10
	Dystonia	9
	Death (suicide)	4
	Symptomatic haemorrhage	3
	Mania or hypomania	2
Transient	Confusion	25
	Depression	23
	Infection/erosion	13
	Mania	11
	Apathy	10
	Psychosis	9
	Seizure	5

[a]Death in the follow-up period; in most cases, death was unrelated to surgery.

Box 1 | On periods and off periods in Parkinson disease

Although medications for Parkinson disease (PD) alleviate symptoms, their benefit can vary in relation to the time of medication and specific symptoms. The times when medications are effectively alleviating parkinsonian symptoms are referred to as on periods, and the times when medications are and not helping are referred to as off periods.

Once electrodes are implanted for deep brain stimulation, the stimulation is continuous, but can be briefly turned off to enable studies of its effects in on periods and off periods. **[Au: Wording OK?]**